REMARKS/ARGUMENTS

The Examiner's attention to the present application is noted with appreciation.

Correction to Claims. The Office Action noted that claim 19 was used twice and claim 22 had been skipped. This formal error is corrected, and it is requested that the amendment be entered. No new matter is introduced thereby.

References to Ohta *et al.* and Andrus *et al.*

The most recent Office Action cites to only abstracts of these articles. Applicant has obtained copies of the articles, and respectfully suggests that the full copies make clearer the difference between Applicant's invention and the cited prior art. Because Applicant is merely providing a full copy of a partial reference cited by the Office, it is believed that no fee is required.

35 U.S.C. § 102(b) Rejection of claims 1, 5, 7-9 and 12 (Office Action at page 4). Claims 1, 5, 7-9 and 12 are rejected as being anticipated by Ohta et al. This rejection is respectfully traversed.

Ohta *et al.* is directed at finding an anticancer drug, and describes DNA polymerase inhibitor KM034. KM034 inhibits the proliferation of the cancer cell line HeLa. The cancer-suppressing effect of KM034 is synergistically enhanced by the addition of bleomycin, described in Ohta, *et al.* as a chemotherapeutic agent. This inhibitor, KM043, also inhibits HIV reverse transcriptase. The examiner suggests that because Ohta *et al.* discloses a virus inhibiting compound (KM034) combined with bleomycin, that this will have an anti-HIV effect. However, nowhere does Ohta *et al.* suggest that the combination has an anti-HIV effect. HeLa cells are cancer model cells, not HIV model cells.

In the present invention, the aim is different. Van Asbeck's invention aims at inhibiting the HIV replication using bleomycin. This is different from killing cancer cells. No remark or suggestion is made or proof is given that bleomycin inhibits HIV-RT or that it is an antiviral drug (as claimed in the invention).

In Ohta *et al.* the cytotoxic effect (as in killing cancer cells) is shown to be synergistically improved

by combining polymerase inhibitor with bleomycin, however, no remark or suggestion is made or proof is given that the synergistic cytotoxic effect of the combination shown for cancer cells also holds for the inhibition of virus replication. The examiner argues at page 4 that since "the cytolytic (lysis of cells) effect of bleomycin is improved," a method of treating HIV infection by bleomycin-induced cytolysis is anticipated. This is not the case, as in the present invention the HIV replication mechanism is affected (it is not a study using cancer cells as a target for the effect of bleomycin). To the contrary, if bleomycin treatment should have cytotoxic effects, this would even worsen the patient's immune system, as already caused by the HIV infection. In addition, Van Asbeck et al. showed that bleomycin at concentrations in which it inhibited viral replication, had no influence at the viability of HIV infected cells (Journal of Infectious Diseases 2000; 181: 484-90 figure 3, see also the application). KM034 combined with bleomycin can be applied as an anti-HIV drug.

In Ohta *et al.* the main agent is a polymerase-inhibitor, where the synergistic other agent is bleomycin. There is no specific reason why bleomycin was chosen. It was only chosen as a chemotherapeutic agent (and certainly not as an anti-HIV agent); it could apparently be any other chemotherapeutic agent.

Ohta *et al.* combined the polymerase inhibitor KM034 with the known anti-cancer effect of bleomycin to get an improved anti-cancer drug. This is not the same as, and therefore does not anticipate, that bleomycin as a virus killer, can be combined with a polymerase inhibitor, and in this form can be used as an improved anti-virus drug, as described in the present invention. Therefore, the present invention and Ohta *et al.* speak about different inventions and Ohta *et al.* does not anticipate the invention of Van Asbeck.

35 U.S.C. § 103 Rejection of claims 1, 3, 4 and 7-11 (Office Action at page 5). Claims 1, 3, 4 and 7-11 are rejected as obvious over Gompels et al. in view of Sham et al. This rejection is respectfully traversed.

In Gompels *et al.* bleomycin (chemotherapeuticum) is combined with vincristine (chemotherapeutic). The Examiner states that the use of bleomycin in conjunction with "Zidovidine (reverse transcriptase inhibitor) therapy is not contra-indicated" in Gompels *et al.* Sham *et al.* teaches that retinavir (protease inhibitor) is used in combination with another virus-inhibiting compound (p. 3 Sham *et al.*). Therefore, it would be obvious to combine compounds to inhibit viruses.

Gompels *et al.* does not apply to the present invention. Gompels *et al.* is aimed at treating Kaposi sarcoma, which may follow as a complication of AIDS, and Gompels *et al.* does not affect the HIV-replication. Kaposi is the consequence of an affected immune system caused by HIV that destroys the cells of the immune system. Therefore the body becomes susceptible to infections, and malignancies such as Kaposi sarcoma. Kaposi sarcoma is not directly induced by HIV. For example, iatrogenic Kaposi sarcoma may develop in patients receiving immuno-suppressive therapy. Epidemic Kaposi sarcoma appears approximately in 21% of homosexual men with AIDS. The etiologic agent appears to be human herpes-virus 8 (HV-8) (DeVita, V.T., Hellman, S. Rosenberg, S.A., Cancer. Principles and Practice of Oncology, 6th edition, Lippincott Williams and Wilkins eds., p 1997, see attached copy). Gompels *et al.* merely describes the treatment of Kaposi using standard chemotherapy, i.e. bleomycin. The anti-HIV treatment he uses is only the standard virus inhibitor ziduvidine. Gompels *et al.* does not describe treatment of HIV infection, with bleomycin alone, nor in combination with ziduvidine. Therefore, Gompels *et al.* does not apply to this invention.

Sham *et al.* mentions the process of combining protease inhibitors in HIV treatment with other anti-HIV treatments such as protease inhibitors or reverse transcriptase inhibitors (Sham *et al.* p 3 last paragraph). The reason for this is that protease inhibitors lose efficiency when applied in monotherapy (Sham, p 2 last lines). Combination treatment *per se* is not obvious, and is not indicated by Sham *et al.* as being obvious, unless a protease inhibitor is used as (main) compound. In Van Asbeck's invention, the primary compound is the radical-producing compound bleomycin, not a protease inhibitor. Another biochemical mechanism is used. That it is "obvious" to combine a protease inhibitor with "another anti-HIV treatment", does not make it obvious to combine bleomycin with a protease inhibitor. Therefore, it is

not obvious to one skilled in the art to incorporate a known efficacious compound in the claimed composition. Claims 1, 3, 4, 7 -11 and 1, 5-9, 12, 13 cannot properly be rejected as obvious, Gompels *et al.* in view of Sham *et al.*

Concerning obviousness over Gompels *et al.* in view of Sham *et al.*, it is further noted that Gompels *et al.* does not describe a combination therapy as such (bleomycin + protease inhibitor) for treatment of HIV infection, nor does the reference describe the treatment of HIV-infection by coincidently combining a protease inhibitor with bleomycin.

Another reason why it is not obvious to combine bleomycin with another compound is that Gompels *et al.* (p1176) describes a combination of two anti-cancer drugs, bleomycin and vincristine, or vinblastine, to treat Kaposi and zidovudine, a known anti-HIV drug, to treat HIV. However, they do not mention an effect on HIV inhibition. This would be a reason not to combine the iron chelator bleomycin with an RT-inhibitor like dideoxyinosine. Therefore, the combination of an iron chelating compound with another compound such as an RT-inhibitor like dideoxyinosine, as currently claimed, is not obvious.

Yet another reason why combination therapy is not obvious is that bleomycin is a toxic compound. It is important to administer as little as possible. Combination with a protease inhibitor or RT-inhibitor might lead to reduction in doses. This is not obvious from Gompels *et al.* nor from Sham *et al.* In Gompels *et al.*, RT-inhibitor and bleomycin do not work on the same target (HIV), so it is not logical to combine them to reduce the dosis doses of bleomycin. In Sham *et al,* the protease inhibitor is combined with other compounds to obviate the limited efficacy in mono-treatment with a protease inhibitor.

35 U.S.C. § 103 Rejection of claims 1, 5-9, 12 and 13 (Office Action at page 6). Claims 1, 5-9, 12 and 13 are rejected as obvious over Gompels *et al.* in view of Sham *et al.* [Malley *et al.*] The Office Action at page 6, second paragraph states the rejection is over Gompels *et al.* in view of Sham et al. However, the following paragraphs discuss Malley *et al.*, and Sham et al. is not discussed. Applicant assumes that the rejection is intended to be as to Gompels *et al.* in view of Malley *et al.*, and responds accordingly. This rejection is respectfully traversed.

The current invention claims a specific combination, i.e. the combination of bleomycin and a reverse transcriptase inhibitor, more specifically dideoxyinosine. Malley *et al.* does describe a combination therapy using dideoxyinosine and hydroxamate derivatives. However, both compounds aim at interfering with the reproduction machinery of HIV. Given the synergistic effects of reverse transcriptase-inhibiting compounds shown in Malley *et al.*, it might have been obvious or motivating to combine a new reverse transcriptase inhibiting compound with dideoxyinosine. However, it is not obvious from Malley *et al.* that the radical-producing agent bleomycin can be combined with dideoxyinosine. Moreover, not all combinations show an advantageous or synergistic effect. Malley *et al.* shows in figure 3B, p 11019, that a combination of ddI/ddC or ddI/AZT showed similar results as hydroxamates DAH or HU. Bleomycin is not a hydroxamate. This makes a synergistic effect with ddI not obvious, given the apparent unpredictable character of synergy. For these reasons, the invention is not obvious over Gompels *et al.* in view of Malley *et al.*

35 U.S.C. § 103 Rejection of claims 14-17 and 20-25 (Office Action at page 7). Claims 14-17 and 20-25 are rejected as obvious over Andrus et al. in view of Sham et al. This rejection is respectfully traversed.

In Van Asbeck's invention, the combination of AIDS inhibitor deferiprone (a hydroxipiridon) (known from Andrus *et al.*) and protease inhibitor ritonavir is claimed in product claims (14-17) and method claims (20-25). Andrus *et al.* describes the hydroxipiridon deferiprone as an inhibitor of the translation machinery of unspliced HIV mRNAs. The present invention describes the use of the hydroxipiridon deferiprone as an iron chelator. Since HIV replicates only in the proliferating cells (Zack et al. Cell 1990; 61:213-22) and proliferative cells have higher needs for iron, it was supposed that iron chelation could inhibit HIV replication as shown in Fig. 2 (Journal of Infectious Diseases 2000; 181: 484-90). Deferiprone indeed inhibited significantly HIV replication and proliferation of peripheral blood lymphocytes. The supposed working mechanism is therefore different. The use of deferiprone as an HIV treatment as taught by Andrus is therefore not the same as the way deferiprone is used in Van Asbeck's invention (i.e. inhibiting

the replication of the HIV infected host cell). Therefore Andrus *et al.* does not apply to the present invention.

Sham does not apply to the current invention, as Sham aims at the obviousness of combining a protease-inhibitor with another compound such as another protease inhibitor or RT-inhibitor. Combination treatment is obvious in Sham *et al.* because a single protease inhibitor is not stable for mono-treatment and therefore not effective. Sham *et al.* does not speak about a more effective treatment, in the meaning of a stronger or even synergistic effect, as a reason for combining substances. Sham *et al.* does not teach that combination therapy is more efficient or obvious in general situations, other than when a weak protease inhibitor is used. Combination therapy would be obvious in view of Sham *et al.* when deferiprone would be an unstable or not effective protease inhibitor or inefficient other compound. In the present invention, the focus of the invention is aimed at a synergistic effect.

The combination of deferiprone with another compound for reasons of a multi-target (synergistic) approach is never mentioned or suggested in the literature, and specifically not in Andrus *et al.* Therefore, it is not obvious.

The non-obviousness of combination therapy in view of Sham *et al.* furthermore appears from the fact that Sham *et al.* claims combination therapy for its own new compounds in its method claims 32 and 34.

It is furthermore not obvious to claim a combination of compounds, as a combination can also result in absence of beneficial effects or even adverse effects. This makes it relevant to investigate possible combinations for an advantageous effect.

35 U.S.C. § 103 Rejection of claims 14, 15, 18-23, 26 and 27 (Office Action at page 8).

Claims 14, 15, 18-23, 26 and 27 are rejected as obvious over Andrus et al. in view of Malley et al. This rejection is respectfully traversed.

Andrus *et al.* describes the working of deferiprone as an anti-HIV treatment, but via a different working mechanism (see above).

Malley *et al.* shows a combination of RT-inhibitors. However, in Van Asbeck's invention, a combination of hydroxipirodon with RT-inhibitors is not obvious. Not all combinations show an advantageous or synergistic effect. Malley *et al.* shows in figure 3B, p 11019 that a combination of ddI/ddC or ddI/AZT showed similar inhibition profiles to ddI alone, but synergistic increases when combined with hydroxamates DAH or HU. A hydroxipyridinon, as claimed in Van Asbeck's claim 14, is not a hydroxamate. This makes a synergistic effect with ddI not obvious, given the apparent unpredictable character of synergy.

From the current invention, it becomes clear that a combination of an iron chelating compound with RT-inhibitor has beneficial effects on HIV treatment.

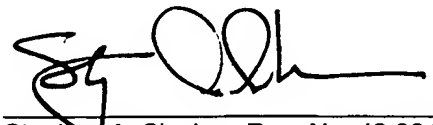
Gompels *et al.* (p 1176) describes a combination of two anti-cancer drugs, bleomycin and vincristine or vinblastine, to treat Kaposi, and Zidovudine, a known anti-HIV drug, to treat HIV. However, they do not mention an effect on HIV inhibition. This would be a reason not to combine the iron chelator bleomycin with an RT-inhibitor like dideoxyinosine. Therefore, the combination of an iron chelating compound with another compound such as an RT-inhibitor like dideoxyinosine, as currently claimed, is not obvious.

Conclusion. In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

If any issues remain, or if the Examiner believes that prosecution of this application might be expedited by discussion of the issues, the Examiner is cordially invited to telephone the undersigned attorney for Applicant at the telephone number listed below.

Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213.

Respectfully submitted,

By: 

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